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EXAMINER	
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ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/673,448	CLARK ET AL.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *4/19/04; 4/21/04*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14,17-34,49 and 50* is/are pending in the application.

4a) Of the above claim(s) *49 and 50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14 and 17-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed April 21, 2004 and April 19, 2004. Currently, claims 1-14, 17-34, 49-50 are pending. Claims 49-50 have been withdrawn as drawn to non-elected subject matter.

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 19, 2004 has been entered.

3. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.

4. Any objections and rejections not reiterated below are hereby withdrawn in view of the amendments to the claims or applicant's remarks.

5. This action contains new grounds of rejection necessitated by amendment.

Priority

6. This application claims priority to PCT/AU99/00306, filed April 23, 1999 and Australian PP 3129, filed April 23, 1998.

It is noted that the priority document does not appear to contain support for differential methylation in liver cancer tissue DNA extracts. Figure 9 of the instant application appears to be first present in the PCT/AU99/00306. Therefore, Claims

directed to liver cancer are not supported by the Australian PP 3129 document and receive the benefit of April 23, 1999.

The examiner has reviewed the priority document with respect to the presence of liver cancer. While there is no intervening art on record and therefore the observation does not appear to affect any of the rejections of record, the teachings in the priority document do not provide an enabling disclosure that liver cancer contains differential methylation.

Information Disclosure Statement

7. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

New Grounds of Rejection Necessitated by Amendment

New Matter

8. Claims 1-14, 17-34 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In the amended claims, reference to "defined by (and inclusive of) sites 342-343 of SEQ ID NO: 52 to CPG sites 581-582 of SEQ ID NO: 54" are included. The amendment does not appear to point to support for the new claim language. The specification does not describe or discuses "defined by (and inclusive of) sites 342-343 of SEQ ID NO: 52 to CPG sites 581-582 of SEQ ID NO: 54". The specification does not appear to contemplate nucleotides 342-343 of SEQ ID NO: 52 and 581-582 of SEQ ID NO:54. The concept of "defined by (and inclusive of) sites 342-343 of SEQ ID NO: 52 to CPG sites 581-582 of SEQ ID NO: 54" does not appear to be part of the originally filed invention. The specification does not appear to specifically delineate nucleotides 342-343 of SEQ ID NO: 52 and 581-582 of SEQ ID NO:54 of these sequences. Furthermore, as written it is unclear how a region may be defined by 2 nucleotides to 2 nucleotides of SEQ ID NO: 54. The specification does not appear to indicate how SEQ ID NO: 52-54 are related. Moreover, it is not clear what is meant by this recitation (see 112/2nd below). Therefore, "defined by (and inclusive of) sites 342-343 of SEQ ID NO: 52 to CPG sites 581-582 of SEQ ID NO: 54" constitutes new matter. Applicant is required to cancel the new matter in the reply to this Office Action.

Further, with respect to "wherein the isolated DNA is not treated with a methylation sensitive restriction endonuclease prior to amplification in step (i)" the specification does not appear to have basis for this negative limitation. The instant response does not appear to point to any support in the specification for this newly added recitation. It is noted that the specification teaches methods which do not positively recite using a methylation sensitive restriction endonuclease prior to

amplification. However, MPEP 2173.05(i) states that "Any negative limitation or exclusionary proviso must have basis in the original disclosure. If alternative elements are positively recited in the specification, they may be explicitly excluded in the claims. See In re Johnson, 558 F.2d 1008, 1019, 194 USPQ 187, 196 (CCPA 1977) ("[the] specification, having described the whole, necessarily described the part remaining."). See also Ex parte Grasselli, 231 USPQ 393 (Bd. App. 1983), aff 'd mem., 738 F.2d 453 (Fed. Cir. 1984). The mere absence of a positive recitation is not basis for an exclusion." The instant specification does not provide alternative elements positively recited for "wherein the isolated DNA is not treated with a methylation sensitive restriction endonuclease prior to amplification in step (i)" nor does the original specification teach the negative limitation. It is noted that on page 4, lines 15-16, the specification states that "the method relies on selective amplification of a target region of the GST-Pi gene but does not require prior restriction with an informative restriction enzyme." The instant specification does not appear to define "informative restriction enzyme. An informative restriction enzyme thus may encompass any sensitive or resistant methylation restriction endonuclease in addition to all other restriction enzymes which provide information of particular sequences within a nucleic acid. Thus, by reading this passage in the instant specification, the skilled artisan would not conclude that an informative restriction enzyme was a methylation sensitive restriction enzyme. Thus, the negative limitation appears to constitute new matter.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-14, 17-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A1) Claims 1-14, 17-34 are indefinite because it is unclear what "within the region of the GST-Pi gene and/or its regulatory flanking sequences defined by (and inclusive of) sites 342-343 of SEQ ID NO: 52 to CpG sites 581-582 of SEQ ID NO: 54" encompasses. It is unclear whether the claim is drawn to a region between SEQ ID NO: 52 and 54 (however it is unclear how these two nucleic acids are related to one another) or whether the claim is drawn to the four particular enumerate nucleotides. It is unclear what region is defined by SEQ ID NO: 52 to SEQ ID NO: 54. The instant specification does not provide how these sequences are related. As written, the metes and bounds of the claimed invention are unclear. Further, Claims 18-25, 31-34 are each directed to particular CpG sites which are not defined by particular sequences. The claims, for example recite –43 to +53, however, this is not in relation to any particular SEQ ID NO:. Further it is unclear how these numbers relate to any particular sequence within the specification. Sequences do not have "-" positions when written in SEQ ID NO: form. Therefore, it is unclear what CpG sites –43 to +53 correspond to in relation to a SEQ ID NO:.

B1) Claims 1-14, 17-34 are indefinite over the recitation "prior to amplification in step (i)" because step (i) does not contain an amplification step. It is noted that step (ii) is directed to an amplification step. Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1-14, 17-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al (Cancer Epidemiology, Biomarkers, Prevention. Vol. 6, pages 443/450, June 1997) in view of Herman et al. (US Pat. 5,786,146, July 1998).

Lee et al. (herein referred to as Lee) teaches CG island methylation changes near the GSTP1 gene in prostatic carcinoma cells detected using the polymerase chain reaction: a new prostate cancer biomarker. Lee teaches isolating DNA from normal and neoplastic cells and tissue from prostate carcinoma specimens (page 443, col. 2)(limitations of Claim 1 (i), 14-17, 44-47). Lee teaches that the DNA specimens were subjected first to exhaustive digestion with excess HpaII, which cuts the unmethylated sequence (page 443, col. 2). The samples were then amplified using PCR primers (page 443, col. 2)(limitations of Claim 3). As seen in Figure 1, GSTP hypermethylation of the promoter region, -408 to +197 was amplified in the describe method and then further amplified by primers directed to –220 to -57, but GSTP1 hypomethylation in the same region did not yield a PCR product, i.e., the amplification is selective that it only amplifies the target region if the site at which abnormal cytosine methylation occurs is methylated (Claim 1 (ii), 18-25, 35-39). The PCR amplification products are then electrophoresed on polyacrylamide gels and visualized by staining with ethidium bromide or Southern blot hybridization analysis (page 444, col. 1)(limitations of Claim 1 (iii)). Lee teaches that using the PCR assay strategy, more than 90% of human prostatic carcinoma DNA specimens analyzed exhibited deoxycytidine methylation changes extensively encompassing the GSTP1 promoter region (page 443, col. 2).

Lee suggests that bisulfite detection may prove useful as molecular staging and diagnosis strategies (page 449, col. 1). Moreover, Lee teaches that methylated CG dinucleotides can be distinguished from CG dinucleotides at specific genomic DNA loci by several means potentially amenable to use with DNA amplification strategies

including treating amplified DNA with bisulfite to promote selective deamination of C nucleotides to U nucleotides that permits discrimination of C nucleotides from methylated C nucleotides as differences in the nucleotide sequence of the amplification product accompanying bisulfite treatment (page 446, col. 2). Lee does not specifically teach the benefit of using bisulfite treatment for distinguishing methylated DNA from unmethylated DNA.

However Herman et al. (herein referred to as Herman) teaches methylation specific PCR (MSP) for rapid identification of DNA methylation patters in a CpG containing nucleic acid (abstract). Herman reviews numerous ways that methylation had been previously detected, including methylation-sensitive enzymes, Southern hybridization with methylation sensitive restriction enzymes and methylation sensitive enzymes and the PCR (col. 2-3). Herman teaches that each of these methods have drawbacks which makes utizilizing bisulfite treatment of DNA to convert all unmethylated cytosines to uracil followed by PCR advantageous. Herman teaches a method for rapid assessment of the methylation status of any group of CpG sites within a CpG island independent of the use of methylation-sensitive restriction enzymes (col. 3, lines 40-45). Herman teaches that with MSP, all CpG sites, not just those within sequences recognized by methylation-sensitive restriction enzymes may be analyzed (col. 5, lines 1-4). Further MSP also eliminates the frequent false positive results due to partial digestion of methylation-sensitive enzymes inherint in previous PCR methods for detecting methylation (col. 5, lines 5-10). MSP requires only small amounts of DNA, is sensitive to 0.1% of methylated alleles of a given CpG island locus, and can be

performed on DNA extracted from paraffin-embedded samples (col. 3, lines 50-55). MSP eliminates the false positive results inherent to previous PCR-based approaches which relied on differential restriction enzyme cleavage to distinguish methylated from unmethylated DNA (col. 3, lines 55-58). Herman teaches that MSP primers are specifically designed to recognize CpG sites to take advantage of the differences in methylation to amplify specific products to be identified by the invention assay (col. 4, lines 55-60). Herman compares MSP to the only technique that can provide more direct analysis, namely genomic sequencing. MSP is much simpler and requires less time than genomic sequencing, avoids the use of expensive sequencing reagents and the use of radioactivity, and increased sensitivity (col. 5, liens 15-30). The MSP method comprises contacting a methylated CpG containing nucleic acid specimen with an agent that modifies unmethylated cytosine, amplifying the CpG containing nucleic acid in the specimen by means of CpG-specific oligonucleotide primers and detecting the methylated nucleic acid (col. 5, lines 40-47). Herman teaches that the preferred agent for modifying unmethyalted cytosine is sodium bisulfite (limitations of Claim 2, 8, 40-41). Herman teaches that cytosine reacts with the bisulfite ion to form a sulfonated cytosine reaction intermediate which is susceptible to deamination, giving rise to a sulfonated uracil (col. 5, lines 60-62). Uracil is recognized as a thymine by Taq polymerase and therefore upon PCR, the resultant product contains cytosine only at the position where 5-methylcytosine occurs in the starting template DNA (col. 5, lines 63-67)(limitations of Claim 4-5). Herman teaches that the method of amplifying is by PCR preferably (col. 8, lines 58-59)(limitations of Claim 9). Herman teaches that the primers specifically

distinguish between untreated DNA, methylated and non-methylated DNA. MSP primers usually contain relatively few Cs or Gs in the sequence since the Cs will be absent in the sense primer and Gs absent in the antisense primer (col. 6, lines 5-10)(limitations of Claim 7, 10, 11, 13). The primers typically contain 12-20 or more nucleotides, although they may contain fewer nucleotides (col. 6, lines 34-37)(limitations of Claim 6, 12). Herman teaches that any specimen in purified or nonpurified form can be used. The specimen may be from any source including prostate, lung (col. 7, lines 30-35). The nucleic acid is in the region of the promoter of a structural gene typically (col. 10, lines 17-19). Herman teaches that the detection of the methylated CpG containing nucleic acid in the specimen may be indicative of cellular proliferative disorder or neoplasia including prostate cancer.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to have modified the methylation detection method of Lee with the methylation detection method of Herman. The ordinary artisan would have realized based upon the explicit teachings of Herman, that the method of using methylation specific primers was advantageous over digestion with methylation-sensitive enzymes followed by PCR. Herman specifically states, "MSP eliminates the false positive results inherent to previous PCR-based approaches which relied on differential restriction enzyme cleavage to distinguish methylated from unmethylated DNA". Herman also additional advantages of using MSP detection methods as compared to other methylation detection methods. MSP detection uses isolated DNA which is not treated with a methylation sensitive restriction endonuclease prior to amplification, which is exactly

what is being claimed. Herman specifically points out the desirability of using MSP to avoid the use of enzymes. Since Herman has specifically compared the methylation detection method of Lee with the modified methylation detection method of Herman and found that the MSP methylation detection method has benefits, the ordinary artisan would have been motivated to have used the MPS methylation detection method. Therefore, the ordinary artisan would have been motivated to have modified the method of detecting methylation in the promoter region of Lee with the MSP methylation detection method of Herman for the explicit benefits taught by Herman.

Response to Arguments

The response traverses the rejection. The response asserts that the amendments to the claims to exclude exhaustive digestion render the rejection moot. This argument has been thoroughly reviewed, but is not found persuasive because the precise changes made to Lee is the method which requires exhaustive digestion to a method which does not rely upon enzymes for digestion and provides the clear benefits and improvements for the MSP method. Thus, the rejection is not rendered moot and is directed specifically at the motivation to modify the digestion steps in Lee.

In the previous response dated February 6, 2003, the response asserts that Lee does not teach nor suggest the present invention. This argument has been reviewed but is not convincing for the reasons presented above. Furthermore, combining the methods of Lee and Herman would be directed to a selective amplification method.

The response dated February 6, 2003 argues that Herman detection method is based upon primers that can distinguish between methylated and unmethylated CpG

sites. The response asserts that this is not abnormal methylation. This argument has been thoroughly reviewed, but is not found persuasive because abnormal methylation causes normally unmethylated CpG sites to become hypermethylated in disease states or alternatively normally methylated CpG sites to become hypomethylated. Therefore, methylation and unmethylation are indicative of abnormal methylation patterns.

The response dated February 6, 2003 focuses on the ability of Lee to simultaneously detect all 12 recognition sequences for HpaII and MSP1 in a sample DNA. The response further poses the question of what the result would be for the modification of detecting methylation in the promoter region of Lee with the MSP method of Herman. The response points out, correctly, that the primers need to be in close proximity to the CpG sites. The ordinary artisan would have clearly recognized this aspect of the MSP method from the teachings of Herman. Moreover, the teachings of Lee include methylation CpG sites over a large region. The ordinary artisan would have recognized that several different amplifications may need to be performed to analyze the complete region. Herman teaches examining regional aspects of CpG island methylation (col. 14). Herman also teaches that MSP allows examination of all CpG sites, not just those within sequences recognized by methyaltion sentisitve enzymes; MSP elemintates the frequent results due to partial digeetions. Moreover, Herman specifically compared the methylation detection method of Lee with the modified methylation detection method of Herman and found that the MSP methylation detection method has benefits, the ordinary artisan would have been motivated to have used the MPS methylation detection method. The suggested "primer" of several

hundred nucleotides in length is not how Herman solves the problem of multiple CpG sites. The primers of Herman "preferably have a T in the 3' CG pair to distinguish it form the C retained in the methylated DNA." Therefore, it is clear from Herman that various primer pairs are used to distinguish between methylated or unmethylated, i.e. abnormal methylation. A single primer is not used to distinguish all recognition sites in a promoter region as suggested by the response.

The response dated February 6, 2003asserts that the ordinary artisan would "not have seen the relevance of Herman's MSP method based on oligonucleotide primers to the detection of the extensive methylation marker taught by Lee et al." (page 19 of response). This argument has been thoroughly reviewed, but is not found persuasive because Herman teaches using multiple primer pairs for different methylation sites. Moreover, Lee strongly suggests that using bisulfite treated DNA can discriminate between C nucleotides and methylated C nucleotides as differences in amplification. Therefore, given the expected benefits taught by Herman for using MSP, the ordinary artisan would have been motivated and expected use the improved MSP method over the digestion methods.

Lee teaches that the CpG sites within the region of the GST-Pi gene and/or its regulatory flanking region can be sued as a marker for prostate cancer. Thus for the reasons above and those already of record, the rejection is maintained.

12. Claims 26-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al (Cancer Epidemiology, Biomarkers, Prevention. Vol. 6, pages 443/450, June

1997) in view of Herman et al. (US Pat. 5,786,146, July 1998) as applied to Claims 1-25, above and further in view of Jhaveri (Gene, Vol. 210, pages 1-7, March 1998) and Morrow et al (Genbank Accession Number M24485, December 1994).

Neither Lee nor Herman teach the specific primers for the amplification of the CpG island of GST-Pi.

However, Jhaveri et al. (herein referred to as Jhaveri) teaches the regions of GST-Pi which are methylated. Jhaveri teaches that the CpG island spans the proximal promoter and the first and second exon and intron.

Morrow teaches the full GST-Pi sequence which includes the proximal promoter, the first and second exon and intron.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to have modified the primers taught by Lee to obtain additional primers for amplification of the CpG island. The ordinary artisan would have recognized based upon the teachings of Jhaveri that one would desire amplifying the proximal promoter, first and second exon and intron. Given the full GST-Pi sequence, the ordinary artisan would have been able to have generated primers which flank these sequences or are directed to specific subsequences within the CpG island for amplification and analysis of the CpG island which allows diagnosis of prostate cancers. Therefore, the instantly claimed primer pairs are functional equivalents to the primer pairs taught by Lee in view of Herman. Herman teaches the general design of MSP primers. Namely, Herman teaches MSP primers usually contain relatively few Cs or Gs in the sequence since the Cs will be absent in the sense primer and Gs absent in the antisense primer (col. 6,

lines 5-10). The primers typically contain 12-20 or more nucleotides, although they may contain fewer nucleotides (col. 6, lines 34-37). Therefore, taking the primers taught by Lee in view of Herman and obtaining alternative functional equivalents which may also amplify the CpG island regions of interest, taught by Jhaveri, would have been well within the guidance provided in the art for the ordinary artisan. The art provides a specific region to design primers to for the detection of methylation, provides how to generate primers which will differentiate methylated nucleic acids from unmethylated nucleic acids and provides a clear advantage of using MSP primers for the differential methylation detection. Therefore, the instant primers of SEQ ID NO: 1-16 are merely functional equivalents for those already taught in the art. Since the claimed oligonucleotides simply represent functional equivalents concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited reference in the absence of secondary considerations.

Response to Arguments

The response traverses the rejection. The response asserts that Jhaveri and Morrow do not provide the deficiencies from Lee and Herman. This argument has been reviewed but is not convincing for the reasons discussed above.

Thus for the reasons above and those already of record, the rejection is maintained.

13. Claims 30-34, are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al (Cancer Epidemiology, Biomarkers, Prevention. Vol. 6, pages 443/450, June

1997) in view of Herman et al. (US Pat. 5,786,146, July 1998) as applied to Claims 1-25, above and further in view Tchou et al (Hepatology, Vol. 28, No. 4, pages 47, October 1998).

Lee in view of Herman does not specifically teach detecting hypermethylation in GST-Pi as an indicator of liver cancer (hepatocellular carcinoma).

However, Tchou et al. (herein referred to as Tchou) teaches the role of GST-Pi expression in hepatocarcinogenesis. Given the teachings that GST-Pi is hypermethylated in prostate cancer, Tchou hypothesized the same phenomenon may occur in HCC. Tchou teaches that CpG methylation is a common phenomenon in HCC. Using PCR-based methylation assay, none of the normal tissues have evidence of CpG methylation near the promoter, however, 18 of 20 tumors showed methylation in that region.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to have modified the teachings of Lee in view of Herman for detecting prostate cancer based upon differential methylation of GST-Pi with the teachings of Tchou that GST-Pi is also hypermethylated in hepatocellular carcinoma. Therefore, the ordinary artisan would have been motivated to have applied the PCR-based methylation method for screening for liver cancer using the same assay as taught in the art for prostate cancer. The ordinary artisan would have been able to have taken samples from the two organs and performed analysis on each of the samples to obtain a more comprehensive analysis of the patients cancer status.

Response to Arguments

The response traverses the rejection. The response asserts that Tchou does not provide the deficiencies from Lee and Herman. This argument has been reviewed but is not convincing for the reasons discussed above. Thus for the reasons above and those already of record, the rejection is maintained.

Conclusion

14. No claims allowable.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272-0745.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

J. Goldberg

Jeanine Goldberg
Patent Examiner
June 30, 2004